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Review

Photorejuvenation – Topical Photodynamic Therapy as Therapeutic Opportunity for Skin Rejuvenation

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A B S T R A C T

The intrinsic aging process of the skin in unavoidable and depends on the passage of time per se. Among harmful environmental factors that contribute to extrinsic aging, long-term effects of repeated exposure to ultraviolet radiation are the most significant and are referred to as photoaging. Photoaging is directly correlated to the quantity of UV rays received during the course of a lifetime. Topical photodynamic therapy is well-established procedure for the treatment of actinic keratoses, Bowen disease and basal cell carcinomas. Clinical experience has demonstrated that extensive treatment of actinic keratoses on sun-damaged skin also produces as a positive side effects significant improvement of the signs of skin aging. An improvement of lentigines, skin roughness, fine lines, increases in skin smoothness and improvement of actinic elastosis, skin colour and reduction of hyperpigmentation were seen. The reversible side effects of photodynamic therapy include pain, erythema, oedema, scaling and crusting, and sometimes in darker skin types post-inflammatory hyperpigmentation. Photodynamic therapy is promising approach for treatment of photoinduced skin aging and takes place between ablative and non-ablative methods for skin rejuvenation. Effective improvement of photoaged skin, the possibility of repeated treatments and imitated side effects makes photodynamic therapy a promising procedure for skin rejuvenation.

Key words: *photoaging, photodynamic therapy, photosensitizer, photorejuvenation*

Introduction

The sun emits visible light, infrared radiation, and UV rays. Exposure to sun with living in an oxygen-rich atmosphere causes unwanted photodamage. In addition, an increasing number of people are exposed to artificial source of ultraviolet radiation used in industries, commercial settings and leisure activities. Having a suntan has long been synonymous with beauty and good health in our culture. Individuals who have outdoor lifestyles, live in sunny climates, and are lightly pigmented will experience the greatest degree of photoaging[1].

Topical photodynamic therapy is a well-established procedure for the treatment of actinic keratoses, Bowen disease and superficial and nodular basal cell carcinomas.

Clinical experience has demonstrated that topical photodynamic extensive treatment of actinic keratoses on sundamaged skin also produces as a positive side effect significant improvement of the signs of skin aging – lentigines, skin roughness, fine lines, increases in skin smoothness and improvement of actinic elastosis, skin colour and reduction of hyperpigmentation were seen[2].

Photoaging

Chronological aging depends on the passage of time per se. Photoaging depends primarily on the degree of sun exposure and skin pigment. It is directly correlated to the quantity of UV rays received during the course of a lifetime. The effects of photodemage are often evident many years before intrinsic aging is apparent.

Photoaging affects the sun-exposed areas and is characterized clinically by fine and coarse wrinkling, roughness, dryness, laxity, teleangiectasia, loss of tensile strength and pigmentary changes. There is also an increase in development of benign and malignant neoplasms on photoaged skin.

Photoaging is a multisystem degenerative process that involves the skin and skin support system. The skin support system includes the bone, cartilage, and subcutaneous compartments, which provide the architectural sup-

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port for dermis, epidermis, and stratum corneum[3]. Subcutaneous facial fat is removed and loss probably to lower growth hormone levels[4]. The structural destruction and loss of dermal collagen fiber bundles leads to wrinkling; irregular melanization leads to lentigines, poikiloderma, and melasma. In skin with long-term sun exposure, the ratio of melanocyte density is approximately twice that of nonexposed skin[5]. Prominent teleangiectasias lead to erythema, and loss of hydratation in stratum corneum leads to fine wrinkling.

When the skin is chronic exposure to UV rays, the epidermis responds with hypertrophy. The stratum corneum thickens, epidermis becomes acanthotic, and there is progressive dysplasia with cellular atypia, and anaplasia. Keratinocytes are irregular with a loss of polarity. Melanocytes are irregular with pockets of increased and decreased numbers. The Langerhans cell population in the epidermis is reduced and that contributed to an impaired immune response to skin cancer[6,7]. The roughness of photoaged skin is result of combination of changes in stratum corneum and changes in the glycosaminoglycan content of the dermis. With age, there is a decrease in glycosaminoglycans in the dermis. In photoaged skin there is paradoxical increase in glycosaminoglycans when compared with intrinsically aged skin. However, there are deposited on the abnormal elastotic material rather than in the papillary dermis and that location may make them unavailable as a source of hydratation[8]. Photoaged skin display thickened basement membrane. Dermal changes in photoaged skin are reduction in collagen and precursors of types I and III collagen, a degeneration of elastic fibres, which are replaced in time by an amorphous mass and chronic inflammation with an increase in degranulated mast cells, macrophages, and lymphocytes[9]. Blood vessels are dilated and tortuous[6]. In addition, because of the diminution of the collagen framework, the blood vessels are poorly supported; they can easy rupture, resulting in solar purpura.

For a photochemical reaction to occur in the skin, ultraviolet radiation from the sun must be absorbed by chromophore, beginning a series of photochemic reactions. Chromophores are DNA, aromatic amino acids, 7-dehydrocholesterol, cytochromes, melanin and bilirubin[3,10]. These reactions can result in changes DNA, including oxidation of nucleic acids and modify proteins and lipids, resulting in changes in function. Their accumulation may result in skin cancer or photoaging changes[1].

Photodynamic therapy

Photodynamic therapy (PDT) involves the activation of a photosensitizing drug, which preferentially localizes to diseased skin, by irradiation with light to cause selective cytotoxic damage[2].

PDT is a two step procedure. In the first step, the photosensitizer is administered to the patient, and it is allowed to be taken up by the target cells. The second step involves the activation of the photosensitizer in the presence of oxygen with a specific wavelength of light directed toward the target tissue. Because the photosensitizer is preferentially absorbed by hyperproliferative tissue and the light source is directly targeted on the lesional tissue, PDT achieves dual selectivity, minimizing damage to adjacent healthy structures[11].

The most commonly used photosensitizers in photodynamic therapy are 5-aminolevulinic acid (ALA) and methylaminolevulinate (MAL).

All light source with suitable spectral characteristics and a high output at an absorption maximum of the photosensitizer can be used for photodynamic therapy[12].

The light sources of PDT can be categorized as conventional light sources and lasers. Lasers by definition are monochromatic light sources. Diode lasers (632 and 670 nm) and pulsed dye lasers (595 nm) have been used in PDT. As that lasers emit coherent light, they can be focused on to even very small target areas with sharp boundaries and greater precision[13,14].

In the treatment of large skin lesions, noncoherent light sources are superior to laser systems because of their large illumination fields. Polychromatic light sources allow the use of different photosensitizers with different absorption maxima. Given the right dose of drug and light, noncoherent light sources appear to be effective as laser sources[12].

Many different light sources can be effectively used in PDT including those that emit blue (410 nm), yellow (595 nm), or red (630 nm) light[15]. The most widely accepted application of ALA PDT is with blue light (410 nm)for the treatment of actinic keratoses. MAL PDT involves exposure to 37 J/cm2 or 75 J/cm2 of red light[14].

The photodynamic therapeutic process involves the topical application of 5-aminolevulinic acid, which is the precursor molecule in the heme biosynthesis pathway from which protoporphyrin IX is formed after several enzymatic reactions. Topical application of ALA penetrates the epidermis and is then converted to protoporphyrin IX, a photosensitizing molecule with preferential formation and accumulation in tissues known to have a high cellular turnover, such as tumor or photodamaged cells. When protoporphyrin IX is photoactivated by an appropriate laser or light source, reactive oxygen species are produced which are toxic to epidermal cells, causing cell lysis. Clinically, erythema and desquamation ensue with the eventual appearance of smoother skin. The absorption spectrum of protoporphyrin IX allows for a wide range of electromagnetic radiation options within the visible spectrum[15].

Photorejuvenation

Clinical experience has demonstrated that PDT extensive treatment of actinic keratoses on sun-damaged skin also produces as a positive side effect significant improvement of the signs of skin aging. In studies on the treatment of actinic keratoses it was observed that after PDT not only did actinic keratoses regress, but that the signs of

skin aging also appeared markedly improved[16,17]. PDT can achieve an improvement of dyspigmentation, skin roughness, fine lines and complexion as well as an increase in skin smoothness and a reduction of actinic elastosis[18–22].

A significant reduction of the epidermis thickness, elastotic material and the dermal inflammatory infiltrate as well as an increase of collagen and procollagen type I and III in the upper dermis were observed. Transforming growth factor beta, which stimulates fibroblast proliferation and thus increases collagen synthesis, was significantly increased after PDT, as well as the transforming growth factor beta type II receptor. The expression of collagen- and elastin-degrading matrix metalloproteinases (MMP-1, -3 and MMP-12) declined in contrast[16]. The expression of p53, an early marker of epidermal carcinogenesis that is not expressed in normal skin, was significantly reduced after PDT so PDT can reverse the process of carcinogenesis in photodamaged skin[23]. Histologically, a significant reduction in degree and extent of keratinocyte atypia, a significant increase in collagen content of the skin and a reduction of solar elastosis were observed. The increase of MMP-1 and procollagen I were not significant. That result suggests that PDT with a reduction of keratinocyte atypia and reduced expression of p53 results in a reduction of the carcinogenic potential in photodamaged skin. The significant increase of collagen and the reduction of solar elastosis explain the clinically observed skin-rejuvenating effects of PDT[16].

Pre-treatments can increase the efficacy of PDT both in curative as well as in aesthetic use. They can synergistically support the treatment effect or improve penetration of the photosensitizer (microneedling, fractional lasers, chemical/ mechanical peeling). Alternatively, pre-treatment with an ablative fractional laser system (CO_2 or Er:YAG laser) can be performed. Non-ablative fractional laser systems do not improve penetration[24]. They are not necessary and vary depending on location, skin type/ skin aging type and extent of extrinsic (particularly UV induced) skin damage.

A single treatment is not always sufficient for cosmetic indications. A second or third treatment at intervals of at least 4 weeks is recommended depending on the side effects of PDT. PDT is possible over the entire year. During the summer months, sufficient sun protection must be assured and in the winter, the incubation phase should be performed in warm rooms since low outdoor temperatures result in reduced enzymatic conversion of the precursors to protoporphyrin IX[25].

Side effects

The phototoxic reactions increase in proportion to longer incubation times, higher photosensitizer concentrations and light doses, with it being unclear, if more intensive PDT regimes actually lead to better cosmetic results. The reversible side effects of PDT include pain, erythema, edema, scaling and crusting, in darker skin types also post-inflammatory hyperpigmentation[26].

Pain develops quickly after the start of irradiation, cumulates during irradiation and decreases again over several hours after irradiation. The pain sensation is dependent on factors such as location (most intense face and scalp), degree of previous sun damage, skin type, gender and disease present (actinic keratoses are more painful than basal cell carcinomas). It varies greatly individually and can be influenced[25].

Conclusions

The multiple procedures are available for treatment of signs of skin aging (laser for treatment of vascular or pigmentary lesions or lasers that induce collagen neosynthesis, high-energy flash lamps, surgical procedures, topical therapies, chemical peelings, fillers, botulinum toxin, and others), but these methods usually improve only one or a few components of skin aging. The simultaneous improvement of numerous components of skin aging in combination with a therapy of possibly existing AK represents the PDT as a good option for skin rejuvenation.

Photodynamic therapy is promising approach for treatment of photoinduced skin aging and takes place between ablative and non-ablative methods for skin rejuvenation. Effective improvement of photoaged skin, the possibility of repeated treatments and imitated side effects makes photodynamic therapy a promising procedure for skin rejuvenation.

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FOTOREJUVENACIJA – MOGUČNOSTI PRIMJENE LOKALNE FOTODINAMSKE TERAPIJE U POMLAĐIVANJU KOŽE

S A Ž E T A K

Intrinzičko ili kronološko starenje kože je neizbježno i ovisi o prolasku vremena. Ekstrinzičko starenje nastaje uslijed djelovanja brojnih štetnih utjecaja okoline od kojih je dugotrajno i opetovano izlaganje ultravioletnim zrakama najznačajnije te uzrokuje fotostarenje kože. Fotostarenje izravno je ovisno o količini UV zračenja primljenog tijekom života. Lokalna primjena fotodinamske terapije je jedan od uobičajnih postupaka u liječenju aktiničkih keratoza, Bowen bolesti i bazocelularnog karcinoma kože. Klinička ispitivanja su pokazala da tretman aktiničkih keratoza u području suncem oštećene kože također dovodi do značajnog smanjenja znakova starenja kože. Dolazi do smanjenja lentiginoznih promjena, smanjenja hrapavosti kože, sitnih bora, poboljšanja teksture kože, smanjenja solarnih elastoza i smanjenja hiperpigmentacija. Nuspojave fotodinamske terapije su bol, eritem, edem, deskvamacija i erozije, a ponekad kod tamnijih tipova kože postupalne rezidualne hiperpigmentacije. Mjesto fotodinamske terapije u liječenju promjena nastalih uslijed foto starenja kože nalazi se između ablativnih i neablativnih metoda pomlađivanja. Njena učinkovitost, mogučnost opetovane primjene i relativno blage nuspojave čine fotodinamsku terapiju obečavajućim terapijskim postupkom za pomlađivanje kože.